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Folates: Supplemental Forms and Therapeutic Applications

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Abstract

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Oral folates are generally available in two supplemental forms, folic and **folinic acid**. Administration of **folinic acid** bypasses the deconjugation and reduction steps required for folic **acid**. **Folinic acid** also appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the **vitamin** in circumstances where folic **acid** has little to no effect. Therapeutically, folic **acid** can reduce homocysteine levels and the occurrence of neural tube defects, might play a role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis, appears to be a rational aspect of a nutritional protocol to treat vitiligo, and can increase the resistance of the gingiva to local irritants, leading to a reduction in inflammation. Reports also indicate that neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome. (Altern Med Rev **1998**;3(3):208-220)

Introduction

Folic **acid** is a water-soluble **vitamin** historically used as a treatment for anemia of

pregnancy. Folates are abundant in the diet; however, these compounds are readily destroyed by cooking or processing. The best food sources of folates are thought to be green-leafy vegetables. Sprouts, fruits, brewer's yeast, liver, and kidney also contain high amounts of folates. Unlike supplemental forms of folic acid, dietary folic acid is a complex and variable mixture of folate compounds. Because dietary folates can be destroyed readily, and since many individuals do not consume high amounts of folate-rich foods, it is thought that folic acid deficiency is one of the most common nutritional deficiencies.

Biochemistry

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Synthesis of the active forms of folic acid is a complex process requiring several enzymes, as well as adequate supplies of riboflavin (B2), niacin (B3), pyridoxine (B6), zinc, and serine (see Figure 1).

Folic acid (vitamin B9) is a member of the B-complex family of vitamins. In plants, folic acid is formed from a hetero-bicyclic pteridine ring, para-aminobenzoic acid (PABA), and glutamic acid (see Figure 2). In the diet, folic acid occurs as complex mixtures of polyglutamate (multiple glutamate molecules attached) conjugate compounds. These compounds tend to be resistant to hydrolysis by enzymes in the gastrointestinal tract; however, a group of zinc-dependent intracellular enzymes (folyl polyglutamate hydrolases) are capable of removing the glutamate groups prior to intestinal absorption.¹

Folic acid is generally well absorbed in humans; however, the process of conversion to the metabolically active coenzyme forms is relatively complex. Folic acid is initially deconjugated in the cells of the intestinal wall to the monoglutamate form. In the liver, this compound is subsequently reduced to dihydrofolate and then to tetrahydrofolate via folate and dihydrofolate reductase. Both of these enzymes require NADPH (niacin dependent) as a cofactor. The next step in the activation of the coenzyme requires the amino acid serine to combine with pyridoxal-5'-phosphate (B6) in order to transfer a hydroxymethyl group to tetrahydrofolate. This results in the formation of 5, 10-methylenetetrahydrofolate (5, 10-methyleneTHF) and glycine. Since it is the precursor of the metabolically active 5-methyltetrahydrofolate (5-MTHF) utilized in the re-methylation of homocysteine metabolism, 5, 10-methyleneTHF is of central importance. Also a precursor to methylidynetetrahydrofolate (used in purine synthesis), 5, 10-methyleneTHF functions on its own in the generation of thymine side chains for incorporation into DNA. The formation of 5-MTHF from 5, 10-methyleneTHF requires the enzyme

methylenetetrahydrofolate reductase (a riboflavin dependent enzyme). After formation of the coenzyme forms of the **vitamin** in the liver, these metabolically active compounds are secreted into the small intestine with bile (the folate enterohepatic cycle), where they are reabsorbed and distributed to tissues throughout the body.

Folinic acid (5-formylTHF), available supplementally as calcium folinate - also known as leucovorin calcium - is an immediate precursor to 5, 10-methyleneTHF. Oral administration of **folinic acid** bypasses the deconjugation and reduction steps required for folic **acid**.

Pharmacology

Although the most common supplemental form of the folates is folic **acid**, it makes up 10 percent or less of dietary folates. The majority of folates in the diet consist of reduced folates and methyltetrahydrofolates. Although folic **acid** is generally well absorbed, evidence suggests that reduced folates and methyltetrahydrofolates are absorbed differently than folic **acid**.

In general, intestinal folic **acid** transport is a saturable process with a pH optimum of 5.5 to 6.0.² Pharmacokinetic studies in pigs indicate oral folic **acid** results in relatively low bioavailability at high doses and has little effect at increasing the metabolically active forms of folic **acid**.³ However, human pharmacokinetic studies indicate folic **acid** has very high bioavailability.^{4,5}

Human absorption kinetic studies of orally administered **folinic acid** have demonstrated a bioavailability of 92 percent.⁶ Following an oral dose of **folinic acid**, the majority of folates are metabolized to 5-MTHF directly during absorption in the intestine, bypassing the need for deconjugation and subsequent reduction in the liver. The net effect on tissues of providing **folinic acid** orally is essentially the same as feeding the coenzyme 5-MTHF.⁷ Evidence also suggests a small amount of **folinic acid** is absorbed systemically when administered as a mouthwash.⁸ **Folinic acid** appears to be a more metabolically active form of folate, possibly capable of boosting levels of the coenzyme forms of the **vitamin** in circumstances, such as psychiatric disorders, where folic **acid** has little to no effect. **Folinic acid** might directly cross the blood brain barrier since reduced folates are actively transported into the brain, whereas folic **acid** is poorly transported to the brain and rapidly cleared from the CNS.^{9,10}

If supplementing with **folinic acid**, oral administration is preferred, since the area under the curve of the active metabolite after intravenous administration is only half that of an oral dose.¹¹ Although oral supplementation of **folinic acid** is a reliable manner of

increasing tissue levels of biologically active folates, intestinal absorption of **folinic acid** is a saturable process. At doses above 20-25 mg of **folinic acid**, the oral and intravenous bioavailabilities of **folinic acid** do not appear to be comparable, with oral administration demonstrating diminished bioavailability when compared to intravenous dosing.¹² Therefore, for doses significantly higher than 25 mg of **folinic acid**, intravenous administration might be preferable.

Folinic acid is prepared pharmaceutically from L-glutamic **acid**, resulting in a calcium salt with equal amounts of diastereoisomers.¹¹ Most commercially available folates are racemic mixtures of R and S isomers about pteridine-carbon 6. Currently, reports are equivocal as to whether unnatural stereoisomers (R isomers) are inert in vivo or whether they modify specific aspects of folate metabolism.¹³ High doses of intravenous and oral **folinic acid** result in different profiles of circulating reduced folates. Oral administration appears to be the favored route of administration for stereoselective drug delivery to the systemic circulation, since intravenous administration is associated with high amounts of both 6S **folinic acid** and 5-MTHF, as well as 6R **folinic acid**. Oral **folinic acid**, on the other hand, has the potential advantage of providing sustained plasma concentrations of 5-MTHF in the absence of significant accumulations of 6R **folinic acid**.¹⁴

A number of drugs can interfere with the pharmacokinetics of folic **acid**. Sulfasalazine, cimetidine and antacids appear to reduce folate absorption.¹⁵ Several drugs, such as aminopterin, methotrexate, pyrimethamine, trimethoprim, and triamterene act as folate antagonists. Although the mechanism is unclear, anticonvulsants, antituberculosis drugs, alcohol, and oral contraceptives produce low serum and tissue concentrations of folate.¹⁶

Folic **Acid** Deficiency

Folic **acid** deficiency is considered to be one of the most common nutritional deficiencies. The following may contribute to a deficiency of folic **acid**: a deficient food supply; a defect in utilization, as in alcoholics and individuals with liver disease; malabsorption; increased needs in pregnant women, nursing mothers, and in cancer patients; metabolic interference by drugs; folate losses in hemodialysis; and an enzyme or cofactor deficiency needed for the generation of active folic **acid**.^{17,18} Absorption of folic **acid** appears to be significantly impaired in HIV disease, irrespective of the stage of the disease.¹⁹ Signs and symptoms of folate deficiency might include macrocytic anemia, fatigue, irritability, peripheral neuropathy, tendon hyper-reflexivity, diarrhea, weight loss, and cerebral disturbances.²⁰

Folic **Acid** and the Treatment of Elevated Homocysteine

A significant component in the pathogenesis, prevention, and treatment of heart disease involves the amino **acid** homocysteine. Increased blood levels of homocysteine are correlated with significantly increased risk of coronary artery disease (CAD),²¹⁻²⁴ myocardial infarction,^{25,26} peripheral occlusive disease,²⁷⁻³⁰ cerebral occlusive disease,^{27,30} and retinal vascular occlusion.³¹ Elevated levels of homocysteine have also been correlated with a variety of other clinical conditions, such as neural tube defects (NTD), nervous system disorders, diabetes, rheumatoid arthritis, and alcoholism.³²

Decreased plasma folate levels are correlated with increased levels of homocysteine, and a subsequent increased incidence of CAD. In a fifteen-year Canadian study of CAD mortality in 5,056 men and women 35-79 years of age, lower serum folate levels were correlated with a significantly increased risk of fatal CAD.³³ In a cohort from the Framingham Heart Study, Selhub et al found concentrations of folate and P5P were inversely related to homocysteine levels and the risk of extracranial carotid-artery stenosis.²⁷

Several studies utilizing folic **acid**, B6, B12, and **betaine**, either alone or in combination, have demonstrated the ability of these nutrients to normalize homocysteine levels.^{28,29,34-36} In a 1994 placebo-controlled clinical study of 100 men with hyperhomocysteinemia, oral therapy with 650 mcg folic **acid**, 400 mcg **vitamin** B12, 10 mg **vitamin** B6, or a combination of the three nutrients was given daily for six weeks. Plasma homocysteine was reduced 41.7 percent ($p < 0.001$) during folate therapy and 14.8 percent ($p < 0.01$) during B12 therapy, while 10 mg B6 did not reduce plasma homocysteine significantly. The combination worked synergistically to reduce homocysteine levels 49.8 percent.³⁷ In 68 patients with recent myocardial infarction, 18 percent had increased plasma homocysteine. Oral folate therapy (2.5 mg) reduced this hyper-homocysteinemia in 94 percent of treated patients (mean decrease 27%).²⁵

Folic **Acid** and Neural Tube Defects

A low dietary intake of folic **acid** increases the risk for delivery of a child with a neural tube defect, and periconceptional folic **acid** supplementation reduces the occurrence of NTD.³⁸⁻⁴⁴ Research also indicates supplemental folic **acid** intake results in increased infant birth weight and improved Apgar scores, along with a concomitant decreased incidence of fetal growth retardation and maternal infections.⁴⁵⁻⁴⁸

Recent work indicates that homocysteine metabolism is likely to be the affected pathway where folic **acid** works to prevent NTD, since significantly higher homocysteine levels have been detected in women carrying affected fetuses than in control women. Evidence

also suggests women with a history of NTD-affected pregnancies have altered folic acid metabolism.⁴⁹⁻⁵² Patients with a severe congenital deficiency of the enzyme methyltetrahydrofolate reductase, which is needed for the formation of 5-MTHF, have reduced levels of both methionine and S-adenosylmethionine in the cerebrospinal fluid and show demyelination in the brain and degeneration of the spinal cord.⁵³⁻⁵⁴ Because of its direct impact in the activation of folic acid to its methyl derivative, a milder version of this enzyme defect is strongly suspected to increase the incidence of NTD.⁵⁵

Cervical Dysplasia

Numerous clinical studies have pointed to an association between folate status in adults and cervical dysplasia,⁵⁶⁻⁵⁸ suggesting that folic acid supplementation might play a role in the prevention of cervical dysplasia. It is thought that low red blood cell folate levels enhance the effect of other risk factors for cervical dysplasia and, in particular, that of human papilloma virus-16 infection.⁵⁹⁻⁶¹ Although folate deficiency might play a role in the initiation of cervical dysplasia, folic acid supplements do not appear to be very effective in altering the course of established disease.

One report suggested folate supplementation might reverse cervical dysplasia in women taking oral contraceptives. Forty-seven young women with mild or moderate dysplasia of the uterine cervix were treated with 10 mg of folic acid orally, or a placebo (ascorbic acid, 10 mg) daily for three months. All women had used a combination-type oral contraceptive agent for at least six months prior to initiation of treatment and continued contraceptive use during the study. Butterworth et al reported biopsy and PAP smear scores improved in the women receiving the folic acid supplementation.⁶²

However, several more recent studies have not shown folic acid supplementation to be an effective approach for reversal of cervical dysplasia.⁶³⁻⁶⁴ In one study, 154 subjects with grade 1 or 2 cervical intraepithelial neoplasia were randomly assigned either 10 mg of folic acid or a placebo daily for six months. No significant differences were observed between supplemented and unsupplemented subjects regarding dysplasia status, biopsy results, or prevalence of human papillomavirus type-16 infection.⁶⁴

Inflammatory Bowel Disease

Evidence suggests folate supplementation might protect against neoplasia in ulcerative colitis. Patients with inflammatory bowel disease (ulcerative colitis and Crohn's) commonly have decreased folate levels, partially due to the use of sulfasalazine, a competitive inhibitor of folate absorption. Lashner et al reported folic acid

supplementation was associated with a 62 percent lower incidence of neoplasia compared with individuals not receiving supplementation. The authors subsequently recommended folate be supplemented during sulfasalazine administration to minimize dysplasia or cancer in ulcerative colitis.⁶⁵

In a more recent report, Lashner et al reviewed the records of 98 patients with ulcerative colitis. Folate use was associated with an adjusted relative risk (RR) for neoplasia of 0.72. Supplementation appeared to have a dose-dependent effect at reducing the odds of neoplasia, with a dose of 1 mg/day reducing the RR to 0.54.⁶⁶

In order to evaluate the efficacy of oral administration of a pharmacological dose of folic or **folinic acid** to prevent folate deficiency in patients with inflammatory bowel disease treated with salicylazosulfapyridine, Pironi et al gave 15 mg/day of either folic or **folinic acid** for one month to two groups of 15 patients with inflammatory bowel disease. Although both folic and **folinic acid** increased body stores of folates, **folinic acid** appeared to be more efficient. After one month the mean increase in red blood cell folate concentration was significantly greater after **folinic acid** therapy than after folic **acid** therapy (910 +/- 383, versus 570 +/- 212 ng/ml; p less than 0.01).⁶⁷

Folic **Acid** and Gout

Although some in vitro evidence suggests folate compounds are potent inhibitors of xanthine oxidase activity,⁶⁸ it appears that pterin aldehydes, a photolytic breakdown product of folic **acid**, is responsible for the observed inactivation of xanthine oxidase.⁶⁹

Because of the ability of the photolytic breakdown product, pterin 6-aldehyde, to inactivate xanthine oxidase, theoretically folic **acid** might have some benefit in the treatment of gout; however, results to date are limited and unimpressive. Folic **acid** administered in doses up to 1000 mg orally a day did not significantly lower serum urate concentration nor decrease urinary urate or total oxypurine excretion in five hyperuricemic subjects.⁷⁰

Anemia

Folic **acid** has a long history of use, in conjunction with **vitamin** B12, for treatment of macrocytic anemia. Recently, several studies demonstrated the efficacy of **folinic acid** for the treatment of nutritional anemia. Thirty patients (20 adults and 10 children) suffering from nutritional anemia were given oral **folinic acid** for 15 days (4-8 mg daily). Supplementation resulted in significant increases in the number of red cells, and in folic **acid** content both in the serum and in the erythrocytes. A decrease of mean corpuscular

hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) was also observed.⁷¹ Lucchi et al gave 4-8 mg of **folinic acid** daily for 25 days to 30 elderly patients suffering from macrocytic anemia. They reported a significant decrease of mean corpuscular volume (MCV) and MCH.⁷²

Vitiligo

In some individuals, administration of folic **acid** appears to be a rational aspect of a nutritional protocol to treat vitiligo. Montes et al observed repigmentation in eight of 15 subjects following prolonged oral administration of folic and ascorbic **acid**, with simultaneous parenteral administration of **vitamin** B12.⁷³

Juhlin and Olsson conducted a two-year study to determine the efficacy of the combination of folic **acid**, **vitamin** B12, and sun exposure for the treatment of vitiligo. One hundred patients with vitiligo were treated, with repigmentation occurring in 52. Total repigmentation was seen in six patients, and the spread of vitiligo was halted in 64 percent of patients. Repigmentation was most evident on sun-exposed areas.⁷⁴

Periodontal Disease

Results indicate folic **acid** can increase resistance of the gingiva to local irritants and lead to a reduction in inflammation.⁷⁵ Pack and Thomson conducted two double-blind studies to evaluate the effects of systemic and topical folate on gingival inflammation during pregnancy. They found folate mouthwash produced significant improvement in gingival health.⁷⁶⁻⁷⁷

A mouthwash containing 5 mg of folate per 5 ml of mouthwash used twice daily for 4 weeks, with a rinsing time of 1 minute, appears to be the most effective manner of application, since the effect of folate on gingival health appears to be moderated largely if not totally through a local influence.⁷⁸

Folate levels should be checked and supplementation with folic **acid** considered in patients on long-term anticonvulsant therapy.⁷⁹ There have been some reports that folic **acid** mouthwash inhibits phenytoin-induced gingival hyperplasia.⁸⁰ However, systemic oral administration of folic **acid** does not demonstrate significant efficacy as the sole therapeutic agent in the reduction of phenytoin-induced gingival hyperplasia.^{81,82}

Psychiatric Applications

Reports indicate neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.^{83,84} Significant deficiencies in folate are also common in the elderly population, and can contribute to a decline in cognitive function.⁸⁵⁻⁸⁷

Patients with major depressive disorder often demonstrate lower serum and RBC folate concentrations. Lower serum folate concentrations are also associated with greater severity of depression.⁸⁸ Some evidence indicates low folate levels can predict poorer response to antidepressant treatment with selective serotonin reuptake inhibitors.⁸⁹ Fava et al found subjects with low folate levels were more likely to have melancholic depression and were less likely to respond favorably to treatment with fluoxetine.⁹⁰ Wesson et al reported patients with higher serum folate levels responded more favorably to the antidepressant medicine desmethylimipramine. They also noted low red-cell folate was correlated with the severity of depression.⁹¹

Clinical recovery in depressed patients with low folate levels has been shown to improve when 5-MTHF is used in conjunction with standard psychotropic medication. Evidence also suggests 5-MTHF can reduce depressive symptoms in patients with normal folate status. Passeri et al compared the effectiveness of an oral dose of 5-MTHF (50 mg/day) and trazodone on depressive symptoms and cognitive status in normofolatemie elderly patients with mild to moderate dementia and depression. After eight weeks of treatment, similar reductions in the Hamilton Depression Rating Scale were observed in the two groups.⁹²

Godfrey et al found that 41 of 123 patients (33%) with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite red-cell folate deficiency. Following a six-month treatment regimen with 15 mg of 5-MTHF or placebo, in addition to standard psychotropic treatment, a greater improvement in outcome scores was observed in the patients receiving 5-MTHF.⁹³

Findings suggest reduced red-cell folate occurs in both phases of bipolar disorders.⁹⁴ Limited evidence also implies supplemental folic acid might positively effect morbidity of some patients placed on lithium prophylaxis.⁹⁵

Botez et al believe unrecognized and treatable folate deficiency might be the basis of a well-defined syndrome of neurologic, psychiatric and gastrointestinal disorders, with restless legs syndrome representing the main clinical expression of folate deficiency in adults. Neuropsychiatric manifestations might appear as mild depression, permanent muscular and intellectual fatigue, mild symptoms of restless legs, depressed ankle jerks, diminution of vibrational sensation in the legs, stocking-type hypoesthesia, and long-lasting

constipation. Their experience indicates an oral dose of 5-10 mg of folic **acid** for 6-12 months can eliminate or control these symptoms.⁹⁶⁻⁹⁸

Because the costs and risks associated with supplementation of low doses of folic or **folinic acid** are relatively small, these nutrients should be considered as adjunctive therapies in the treatment of patients with depression, schizophrenia, unipolar or bipolar affective disorders, and for geriatric patients with mild dementia. Although many of these patients will have limited or no response to the additional folate, a significant minority might have folate-responsive conditions.⁸⁴

Nutrient Interactions

Experimental evidence indicates high doses of retinol enhance the folate-dependent oxidation to CO₂ of formate and histidine, and reduces the activity of hepatic methylenetetrahydrofolate reductase, resulting in decreased 5-methyltetrahydrofolate synthesis. The net result of this interaction could potentially result in decreased ability to regenerate homocysteine to methionine.⁹⁹ Animal experiments indicate diets sufficient in methionine have a sparing effect on folates.¹⁰⁰ Use of pancreatic enzymes might impair absorption of folic **acid**, so it is probably wise to supplement folic **acid** away from these enzymes if both are being used therapeutically.¹⁰¹

Safety and Toxicity

Folic and **folinic acid** are generally regarded as not toxic for humans; however, some concern exists that supplementation might mask a **vitamin** B12 deficiency resulting in neurological injury secondary to undiagnosed pernicious anemia. Several authors have suggested folic **acid** supplements might interfere with intestinal zinc absorption; however, the preponderance of evidence does not support this assertion. At doses as high as 5-15 mg of folic **acid** daily, folic **acid** does not appear to have any significant effect on zinc status in healthy nonpregnant subjects.¹⁰²

Information is limited on the antagonism of drug effects of folates in individuals treated with anti-folate medications. Since these medications are used to treat a wide range of malignant and nonmalignant disorders, cavalier use of folates should be avoided until further investigations are conducted. Folates can impact seizure control in drug-treated epileptic patients, so they should be administered with caution to these individuals.^{102,103}

Conclusion

The two supplemental forms of folate are folic acid and folinic acid. While many practitioners are aware of folic acid, folinic acid has largely been reserved as an agent to be utilized for methotrexate rescue. Folinic acid has several advantages over folic acid which might, under some circumstances, offer a therapeutic advantage. It bypasses several steps in the conversion of folic acid to 5-MTHF, is more readily transported into the central nervous system than folic acid, has a longer half-life in the body, and it appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. The major disadvantage of folinic acid is its increased cost to the consumer.

The two most widely accepted uses of folic acid are in the lowering of homocysteine levels and the prevention of NTD. Several studies utilizing folic acid alone, or in conjunction with B6, B12, and betaine, have demonstrated the ability of these nutrients to normalize homocysteine levels. The use of supplemental folic acid has become a common practice in pregnancy. Most prenatal vitamins now contain adequate levels of folic acid to statistically reduce the occurrence of NTD.

Clinical studies have pointed to an association between folate status in adults and cervical dysplasia. While folic acid supplementation might play a role in the prevention of cervical dysplasia, several recent studies have not shown folic acid supplementation to be an effective approach for reversal of existing dysplasia. It is unknown whether folinic acid might produce a response; however, because it has been shown to have activity in some cases where folic acid is not effective, it is worth investigation.

Evidence suggests folate supplementation might protect against neoplasia in ulcerative colitis. Based on the limited available information, it appears folinic acid might have a therapeutic edge over folic acid in inflammatory bowel disease; however, more research is required to definitively establish if an advantage exists.

In some individuals, administration of folic acid appears to be a rational component of a nutritional protocol to treat vitiligo. Results also indicate folic acid can increase the resistance of the gingiva to local irritants and lead to a reduction in inflammation. This activity appears to be a result of a local action, since systemic administration of folic acid has not been shown to be effective, while the use of folic acid mouth rinse has shown efficacy.

Reports indicate neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome. Based on available information, it seems prudent to instigate a therapeutic trial

of folate supplementation in any patient with neuropsychiatric disease. Since **folinic acid** appears to cross the blood-brain barrier more readily than folic **acid**, in these disorders it might be a more effective form of folate supplementation.

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